#12 4/17/02

Attorney Docket No.: 00.22US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Maes, et al.

Serial No.: 09/773,351 Group Art Unit: 1619

Filed: January 31, 2001 Examiner: Willis, M.

For: Cholesterol Sulfate and Amino Sugar Compositions for Enhancement of Stratum Corneum Function

RESPONSE PURSUANT TO 37 CFR 1.111

The Assistant Commissioner of Patents and Trademarks

Washington, D.C. 20231

Dear Sir:

In response to the Final Action of December 12, 2001, and the Advisory Action dated March 26, 2002, please consider the following remarks regarding the rejections which were maintained therein. The Examiner maintained the rejection of claim 19 under section 112, first paragraph for failing to describe subject matter such that one of ordinary skill in the art would be enabled to make and/or use the present invention. Specifically, the Examiner asserts that the specification lacks enablement for "preventing" damage to the skin. The Examiner's position is based on the reasoning that damage to the skin cannot be adequately predicted such that it is not possible to determine if damage has been prevented. In addition, in response to the submission of other patents using the term "preventing", the Examiner points out that each application is examined on its own merits.

Knowledge of certain factors, such as, for example, chronological aging or overexposure to UV radiation based on studies of the changes in the skin subjected to a specific factor makes it possible to predict damage to the skin. Thus, while damage to the skin cannot be predicted in its entirety, there are specific types of damage that the skin may experience and that are indeed predictable. As an illustration, predictability of the damage to the skin is demonstrated in U.S. Patent No. Re. 36,068. In this document, at columns 3 to 4, the predictable characteristics of sundamaged and aging skin are described. Similar to Re. 36,068, Claim 19 does not broadly describe damage to the skin; but rather, addresses a specific type of damage. In Claim 19 the damage is that which is associated with a reduction or loss of skin barrier function, and the characteristics of this damage are described in the present specification. Specifically, at page 1, line 26 to page 2, line, examples of a compromised skin barrier are provided as being UV-damage, degradation of collagen and elastin, and wrinkling and skin atrophy. Therefore, there is an ability based on knowledge in the art regarding aging and sundamaged skin to permit with great accuracy the prediction of damage

associated with a reduction or loss of skin barrier function. It is important to note that the damage referred to in Claim 19 is not open-ended damage to the skin but instead is limited to damage to the skin's protective barrier function.

The Examiner also reasons that "prevention" of a symptom is not the same as a reduction of a symptom. However, Applicants submit herewith a dictionary definition of the word "prevent." The definition of the word "prevent" as it is defined in the Webster's Encyclopedic Unabridged Dictionary of the English Language ("the Dictionary") at page 1141 means "to keep from occurring." There is no mention of a correlation with reducing the thing that is kept from occurring, presumably because they are two different words. However, if a condition already exists the fact that it is possible to reduce that condition inherently means that it is not occurring any further. One of ordinary skill in the art understands the scope and meaning of the word "prevent" as it used in the present invention. Therefore, Applicants request that the Examiner's rejections based on lack of enablement under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner also maintains in the advisory action that Ribier et al. (U.S. Patent No. 5,650,166; "the '166 reference") in view of Subbiah (U.S. Patent No. 6,150,381; "the '381 reference") renders claims 1 to 20 of the present invention obvious under 35 U.S.C. §103(a) because a mixture includes random solutions and vesicles. In response to Applicants' previous arguments regarding the teachings of the '166 reference, the Examiner points out that the '166 reference teaches the formation of vesicles by mixing. However, the second category of vesicles which is taught as being capable of formation by simple stirring does not teach or suggest a simple mixture of an exfoliant and cholesterol sulfate which are the actives of the present invention. The present invention relates to a mixture of cholesterol sulfate and an exfoliant which can be N-acetylglucosamine. Specifically, the '166 reference teaches N-acetyl-glucosamine as being an active agent with deep down action at column 5, line 67 (i.e., encapsulated in the first category vesicle B) 1 Production of vesicles of first category (diffusing deep down)), it is not taught as a second category active for diffusing at the surface. Therefore, the teaching of second category vesicles containing surface diffusing actives by simple stirring with a lipid system in Table 1 fails to teach or suggest the present invention because N-acetyl glucosamine is not taught in the '166 as being a surface diffusing active.

As the Examiner points out, at column 8, line 23, of the '166 reference, the production of vesicles of the second category (diffusing at the surface) are taught, however, the simple stirring is of the second category active into a particular type of lipid system disclosed in Table 1 which will act as the membrane for the lipid. Thus, while it appears that the vesicle can be formed by simple stirring according to the '166 reference in one of the lipid systems of Table 1, the vesicle is then added to the cosmetic composition which

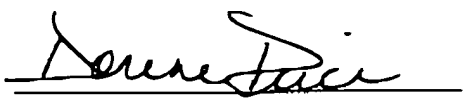
also contains first category vesicles. This is evidenced by the section heading B) Production of the cosmetic composition. Therefore, there is no teaching of a simple mixture of cholesterol sulfate with N-acetylglucosamine in a composition, and thus, no teaching or suggestion of the present invention by the '166 reference.

Further, the '166 reference teaches away from the present invention because the teaching of N-acetyl glucosamine in the '166 reference is as a deep down active which is encapsulated according to the elaborate process in B) Production of vesicles of first category (diffusing deep down). As previously mentioned in the Applicants' Reponse of March 12, 2002, the process of making lipid vesicles taught or suggested by the '166 reference would not provide motivation to one of ordinary skill in the art to make the simple mixture of the present or to achieve the surprising results of the present invention. The '166 reference demonstrates the exact opposite of the present invention. With respect to N-acetyl glucosamine as a deep diffusing active, the '166 reference teaches that co-fusion processing steps are required to make the first category vesicle which is distinguishable over a simple mixture. Further, even if a vesicle can be made as described in the section for second category vesicles by simple stirring, the second category vesicles are still composed of a surface diffusing active encapsulated by a lipid system which is added to a cosmetic. The exfoliant, namely N-acetyl glucosamine, of the present invention is not taught in a simple mixture with cholesterol sulfate, therefore, the '166 reference, alone or in combination with the '381 reference, fails to teach or suggest the present invention. Because neither of the cited references alone nor in combination would lead one of ordinary skill in the art to the compositions and methods of the present invention, a *prima facie* case of obviousness has not been established. Applicants request therefore, that the Examiner's rejection under §103 be withdrawn.

CONCLUSION

In view of the arguments presented above in the present submission, the claims are believed to be in condition for allowance, and issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,



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US00RE36068E

United States Patent [19]

Kligman

[11] E Patent Number: Re. 36,068

[45] Reissued Date of Patent: Jan. 26, 1999

[54] **METHODS FOR TREATMENT OF SUNDAMAGED HUMAN SKIN WITH RETINOIDS**

[76] Inventor: **Albert M. Kligman**, 238 Oceana Dr., Harvey Cedars, N.J. 08008

[21] Appl. No.: **630,872**

[22] Filed: **Apr. 2, 1996**

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: **4,877,805**
Issued: **Oct. 31, 1989**
Appl. No.: **205,057**
Filed: **Jun. 3, 1988**

U.S. Applications:

[63] Continuation of Ser. No. 886,596, Jul. 16, 1986, abandoned, which is a continuation-in-part of Ser. No. 759,505, Jul. 26, 1985, Pat. No. 4,603,146, which is a continuation of Ser. No. 610,711, May 16, 1984, abandoned, which is a continuation-in-part of Ser. No. 297,388, Aug. 28, 1981, abandoned.

[51] **Int. Cl.**[6] **A61K 31/20**

[52] **U.S. Cl.** **514/381**; 514/438; 514/532; 514/559; 514/617; 514/622; 514/725

[58] **Field of Search** 514/381, 438, 514/532, 559, 617, 622, 725

[56] **References Cited**

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Primary Examiner—James H. Reamer
Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas, PLLC

[57] **ABSTRACT**

Various effects of photoaging or sundamage of skin including impairment of differentiation of epidermal epithelial cells and loss of collagen fibers, abnormal changes in elastic fibers and deterioration of small blood vessels in the dermis of the skin are retarded by applying topically to the epidermis in a maintenance therapy program effective amounts of retinoids including retinoid derivatives and stereoisomers thereof such that epithelial growths are substantially reduced and prevented and the skin substantially regains and maintains its firmness, turgor and elasticity. Moreover, with persistent treatment dermal blood cells and vessels increase and the epidermis and dermis thicken, resulting in improved ability of the skin to sense, resist and recover from irritation or injury. Further, hyperpigmentation, lines and wrinkles due to aging are reduced and prevented. The treatment is particularly useful for human facial skin and preferably applied in amounts insufficient to cause excessive irritation.

11 Claims, No Drawings

METHODS FOR TREATMENT OF SUNDAMAGED HUMAN SKIN WITH RETINOIDS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 886,595, filed July 16, 1986, now abandoned, which in turn is a continuation-in-part of my U.S. Pat. Application Ser. No. 759,505, filed July 26, 1985, entitled, "Methods for Retarding the Effects of Aging of the Skin," now U.S. Pat. No. 4,603,146, which was a continuation of application Ser. No. 610,711, filed May 16, 1984, now abandoned, which, in turn, was a continuation-in-part of application Ser. No. 297,388, filed Aug. 28, 1981, entitled "Composition and Method for Improving the Quality of Human Skin and Skin Aging Retardant", now abandoned.

FIELD OF THE INVENTION

This invention relates to methods using retinoids to retard the effects of aging of the skin and generally improve the quality of the skin, particularly human facial skin.

BACKGROUND OF THE INVENTION

Caucasians who have had a good deal of sun exposure in childhood will show the following gross cutaneous alterations in adult life: wrinkling, leatheriness, yellowing, looseness, roughness, dryness, mottling (hyperpigmentation) and various premalignant growths (often subclinical). These changes are most prominent in light-skinned persons who burn easily and tan poorly. The baleful effects of sunlight are cumulative, increasing with time often referred to as "photoaging". Although the anatomic degradation of the skin is most advanced in the elderly, the destructive effects of excessive sun exposure are already evident by the second decade. Serious microscopic alterations of the epidermis and dermis occur decades before these become clinically visible. Wrinkling, yellowing, leatheriness, loss of elasticity are very late changes.

Retinoids (e.g. Vitamin A and its derivatives) are substances which are known to have a broad spectrum of biological activity. Most specifically, these substances affect cell growth, differentiation and proliferation. Retinoids affect the differentiation, maintenance, and proliferation of many types of cells whether they are of ectodermal, endodermal or mesodermal origin; whether they are epithelial, fibroblastic or mesenchymal; or whether they are neoplastic, preneoplastic or non-neoplastic. At present, retinoids have found clinical utility in the treatment of severe cystic acne, psoriasis, and other disorders of keratinization. Possible uses of retinoids are being explored in the prophylaxis and treatment of cancer. For a review of developments in retinoid therapy, see Pawson, B. A. et al. "Retinoids at the Threshold: Their Biological Significance and Therapeutic Potential", Journal of Medicinal Chemistry 25:1269–1277 (1982).

The present status of retinoids in research and clinical medicine can be found in the publication of a symposium held in Geneva: J. H. Saurat. Editor, "Retinoids: New Trends in Research and Therapy," Karger Publishing Co. (1985).

It is known to use certain retinoids, particularly vitamin A acid, topically for treatment of acne as set forth in my U.S. Pat. No. 3,729,568. Other known topical uses of vitamin A acid were reviewed by Thomas, J. R., et al, "The Therapeutic uses of Topical Vitamin A Acid", Journal of American Academy of Dermatology 4:505–516 (1981) include, in addition to acne treatment, treatment of senile comedones, nevus comedonicus, linear verrucous nevus, plantar warts, pseudofolliculitis, keratoacanthoma, solar keratosis of extremities, callosites, keratosis palmaris et plantaris. Darier's disease, ichthyosis, psoriasis, acanthosis nigricans, lichen planus, molluscum contagiosum, reactive perforating collagenosis, melasma, corneal epithelial abrasion, geographic tongue, Fox-Fordyce disease, cutaneous metastatic melanoma and keloids or hypertrophic scars.

It is believed that retinoids influence ultrastructural and proliferative properties of epidermal cells. However, these prior art uses of vitamin A acid have generally involved short term treatments in which relatively high concentrations retinoic acid are applied (i.e. sufficient to cause significant irritation and often peeling) in order to obtain a quick therapeutic effect of the particular condition, such as removal of comedones, as opposed to long-term treatment of normal aging or photographing skin.

My copending application Ser. No. 759,505 discloses methods for treating sundamaged human skin topically with vitamin A acid in an emollient vehicle in such amounts as to be essentially non-irritating to the skin. This treatment causes the skin, particularly human facial skin, to substantially regain and maintain its firmness, turgor and elasticity by retarding and reversing the skin's loss of collagen fibers, abnormal changes in elastic fibers, deterioration of small blood vessels, epidermal atrophy and formation of abnormal epithelial growths.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to the use of other retinoids, as hereinafter defined, in moderating and preventing the aging changes of the exposed (sundamaged) areas of the skin, especially the face. In particular, the methods of the present invention retard the effects of photoaging of the skin due to thinning and abnormal differentiation of the epidermis, inter alia. In general, the present invention relates to methods for retarding and reversing the loss of collagen fibers, abnormal changes in elastic fibers, deterioration of small blood vessels, and formation of abnormal epithelial growths in sundamaged human skin, comprising applying topically to the surface of the skin a composition comprising effective amounts of a retinoid in an emollient vehicle in a program of maintenance therapy, whereby the skin substantially regains and maintains its firmness, turgor and elasticity during the therapy, the composition and amounts of retinoid therein being selected so as to provide a sub-irritating dose for application.

More specifically, the methods comprise the topical application to the surface of the skin of effective amounts of retinoids in a program of maintenance therapy, whereby epithelial neoplasms (basal and squamous cell cancers) and pre-neoplastic growths (actinic keratoses) are substantially prevented. Also, the skin significantly regains and maintains its firmness, turgor and elasticity during the therapy. Effacement of fine wrinkles is an important clinical effect. Generally, the maintenance therapy is begun in adult life when epithelial growths and other aging changes begin to appear clinically. Pigmentary blotching and mottling are also alleviated.

The retinoids may be applied to the skin in any non-toxic, dermatologically acceptable vehicle, preferably a nonvolatile, emollient or lubricating vehicle, in an amount and at a frequency which are insufficient to cause irritation of the skin. Generally, the concentrations are low but may be suitably varied depending on the relative strength of the applied retinoid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The purpose of this invention is to moderate and retard the aging changes in the skin by topical application of retinoids beginning in young adult life when aging characters (sundamage) first become evident clinically. Certain anatomic alterations can be corrected and at least partially reversed, accompanied by improvement in the appearance of the skin.

The invention accomplishes two goals. First, a prophylactic effect in preventing progression and worsening of the damage with the passage of time. Secondly, various abnormalities are corrected and modified to the extent that the structure and function of the skin acquires the characteristics of younger (undamaged) skin.

AGE ASSOCIATED STRUCTURAL CHANGES

Although many of the effects of the aging of the human skin are the result of underlying structural changes which build up over a period of years and can only be detected histologically prior to young adult life, these changes and effects begin to appear clinically in young adults, namely those between about 20 and 30 years of age, and are generally evident about middle age, namely between about 35 and 45 years of age, and become more and more evident and pronounced thereafter, especially in persons excessively exposed to sunlight. The more apparent effects of aging have already been referred to above; and each is associated with one or more underlying structural changes in the skin. For example, blotchiness or mottling (hyperpigmentation) is due to accumulation of melanin in the basal cells of the epidermis. This happens because the reproduction of the cells slows down greatly with aging, allowing them much longer time to receive melanin from the surrounding pigment-producing melanocytes. By stimulating the proliferation of basal cells, pigment retention is prevented.

In addition to obvious cosmetic improvements in the skin, there are a number of other changes which are more important though less apparent, including loss of sensory acuity, reduced wound healing, decreased blood flow and decrease in the thickness of the skin. Older people have less sensitivity to pain and a longer response time. Thus, pain due to irritation or injury is not felt as soon or to the same extent as in young people with the result that superficially minor but potentially serious injuries may be sustained without the individual being aware of the injury until serious damage has occurred.

The surface temperature of the skin in older people is lower than the skin temperature in younger people, so that they often feel cold. This is one reason why the elderly retire to the sun-belt. Anatomically there is a great loss of small blood vessels so that physiologically the blood flow through the skin is greatly reduced. The skin becomes paler and cooler. Furthermore, the decreased blood supply decreases the rate at which irritants and toxins are cleared from the skin. Dangerous build-up of toxic agents can result.

Still further, the skin of older people is more easily torn than that of younger people, since both the epidermis and dermis become thinner with age and the fibrous matrix becomes structurally inferior. As a result, there is less bulk to protect underlying organs and therefore more risk of serious injury. Moreover, when wounds or injuries are sustained, healing of the wounds is much slower in older people.

The underlying causes of the above gross skin effects may be understood more readily from the following discussion of the specific changes in the epidermis and dermis as aging progress

1. Epidermis

With increasing age and exposure of a human to sun and other environmental traumas, cells divide at a slower rate (decreased capacity to renew themselves). They show marked irregularities in size, shape and staining properties; orderliness (polarity) from below to above is lost. The thickness of the epidermis decreases (atrophy). The horny layer which comprises the barrier against water loss and penetration of chemicals becomes abnormal due to the shedding (exfoliation) of cells in large groups or clusters instead of as individual cells, resulting in roughness, scaling and dryness. There is loss of the orderly transformation of living epithelial cells into cornified dead cells which are shed at the surface, that is, differentiation is impaired. Aberrant differentiation results in numerous foci of abnormal epithelial growths or tumors, the most frequent of which are actinic keratoses. After many years these can transform into frank skin cancers called basal cell and squamous cell cancers. Pigment producing cells (melanocytes) can also become altered, forming flat, dark growths (lentigo melanoma) which may progress to malignant melanoma. The cells which make up these permalignant growths are eliminated by topical application of retinoids.

2. Dermis

The cells which make up the fibers of the dermis become smaller and sparser with increasing age, usually in sundamaged facial skin. There is a great loss of collagen fibers resulting in looseness and easy stretchability of the skin; elastic fibers become abnormal so that the skin does not promptly snap back after being stretched. Since the fibrous components comprise more than 90% of the bulk of skin of which 95% is collagen, the degradation of these fibers, especially collagen, is mainly responsible for wrinkling, laxness and loss of elasticity.

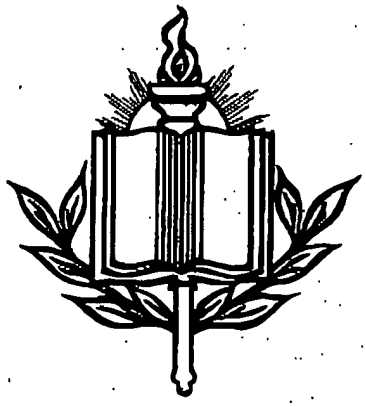
Small blood vessels become thin walled, dilated and often ruptured. Vascular supply thereby becomes compromised.

Beneficial Effects of Retinoids in Accordance With the Present Invention

(a) Increased proliferative activity of epidermal cells. This results in thickening of the epidermis with correction of atrophy. Cell renewal is quickened so that cells divide at a rate typical of younger skin. Treatment with retinoids in accordance with the invention can double the thickness of the epidermis. The stimulation of cell growth also results in faster wound healing. Experiments have been performed wherein blisters have been raised and the roofs cut off of the skins of individuals of various ages. Healing takes place in 2 or 3 weeks in young people, but takes much longer in older persons. Application of the retinoid tretinoin, vitamin A acid or all-trans retinoic acid before raising the blister halves the healing time.

(b) Correction of abnormalities of differentiation. Retinoids regulate and control the physiologic behavior of epithelial tissue, assuring its stability and integrity. They correct and normalize abnormalities of differentiation. In sundam-

Webster's Encyclopedic Unabridged Dictionary of the English Language



The dictionary entries are based on the First Edition of *The Random House Dictionary of the English Language*

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Printed and Bound in the United States of America

Library of Congress Cataloging-in-Publication Data

Webster's encyclopedic unabridged dictionary of the English language.
1. English language—Dictionaries.
PE1625.W46 1989
423—dc19 89-3785
CIP

ISBN 0-517-68781-X

15 14 13 12 11 10 9 8

...nature. See PRETER-, NATURAL ...aldom, pre·ter·nat·u·ral·i·ty (prē/... ...al), pre/ter·nat/u·ral·ness, n. —Syn. ...ual. extraordinary. unnatural. —Ant. 1. ordinary, usual.

...test; v. prē test/), n. 1. a test given to ...student is sufficiently prepared to begin ... 2. a test taken for practice, as a ...study. ...3. to give a pretest to (a student, ...t. 4. to conduct a pretest: The com... ...for consumer acceptance. [PRE- + TEST]

...text), n. 1. that which is put forward ...purpose or object; an ostensible reason: ...the insults as a pretext to declare war. 2. ...appearance or behavior assumed with ...many lavish compliments were a pre... ...mockery. [< L praetext(um) pretext, ...of neut. ptp. of praetexere to pretend, ...front, hence, adorn. See PRE-, TEXTURE] ...rge, evasion.

...tek/stə), n., pl. -tex·tae (-tek/stē).

...n. praetor. —pre·to·ri·al (prē tôr/-... —pre·to/ri·an, adj., n.

...tôr/ē ə, -tôr/-), n. a city in and the ...capital of the Republic of South Africa, in ...the capital of Transvaal. 420,053 (1960).

...tôr/ē ə, -tôr/-; Du. prā tō/Rē ōōs/). ...hel·mus Ja·co·bus (ä/dRēs vil hel/-... ...1799–1853, and his son Mar·thi·nus ...(tē/nōōs ves/əls), 1819–1901, Boer ...men in South Africa.

...ri/əl, -trīl/), Law. —n. 1. a proceeding ...arbitrator, etc., before a trial to simplify ...and fact and stipulate certain matters ...in order to expedite justice and ...the trial. —adj. 2. of or pertaining to ...[PRE- + TRIAL]

...fī/), v.t., -fied, -fy·ing. 1. Often ...make pretty: to prettify a natural beauty. ...or gloss over (something unpleasant): ...current international crisis; an attempt to ...behavior. [PRETT(Y) + -IFY] —pret/-... —pret/ti·fi/er, n.

...adj., -ti·er, -ti·est, n., pl. -ties, adv., ...—adj. 1. pleasing or attractive to ...feminine or childlike way, as by delicacy, ...a pretty face. 2. (of things, places, ...the eye, esp. without grandeur. 3. ...ear: a pretty tune. 4. pleasing to the ...taste: He writes pretty little stories. ...(ironically) fine; grand: This is a pretty ...Informal. considerable, fairly great: This ...him a pretty sum. 7. Archaic or Scot. ...—n. 8. Usually, pretties. a pretty thing. ...9. (used in address) a pretty person: ...pretty. —adv. 10. moderately: Her work ...11. quite; very: The wind blew pretty ...fly Dial. prettily. 13. sitting pretty, ...advantageous position. b. well-to-do; ...14. to make pretty; improve the ...(sometimes fol. by up): to pretty oneself ...pretty up a room. [ME prety, praty, OE ...wily, deriv. of prǣt a trick, wile; ...prank, Icel prettr trick, prettugr tricky] ...—pret/ti·ness, n. —pret/ty·ish, ...

...beautiful. 2. pleasant. 11. fairly, some... ...1. ugly.

...prit/ē fīs/), n. an herb, Brodiaea ...western coast of the U.S., having purple... ...or salmon-yellow flowers.

...ûrē tip/ə fī/), v.t., -fied, -fy·ing. to ...prefigure the type of: The father's ...typified his son's. [PRE- + TYPIFY]

...zəl), n. a crisp, dry biscuit, usually in ...knot or stick, salted on the outside. [< G ...Brezel; cf. ML bracellus bracelet]

...sən), n. German name of Prussia.

...vāl/), v.i. 1. to be widespread or current; ...where or generally: Dead silence prevailed ...route. 2. to appear or occur as the more ...frequent feature or element; predominate: ...prevail in the upholstery. 3. to be or prove ...strength, power, or influence (usually fol. by ...prevailed over their enemies in the battle. 4. ...become dominant; win out: to wish that the ...prevail. 5. to use persuasion or induce... ...fully: He prevailed upon us to accompany ...praevale(re) (to) grow very strong < L ...to) be more able, equiv. to prae- PRE- + ...strong] —pre·vail/er, n. ...ponderate. 3. overcome. —Ant. 3. lose.

...(pri vā/ling), adj. 1. predominant; pre... 2. generally current: the prevailing ...effectual [PREVAIL + -ING²] —pre·vail/ing·ly, adv. —pre·vail/ing·ness, n.

—Syn. 1. preponderant, preponderating, dominant; prevalent. 2. common. See current. 4. effective. —Ant. 2. rare.

prev·a·lent (prev/ə lənt), adj. 1. widespread; of wide extent or occurrence; in general use or acceptance. 2. having the superiority or ascendancy. 3. Archaic. effectual or efficacious. [< L praevalent- (s. of praevalēns), prp. of praevalēre to PREVAIL. See PRE-, -VALENT] —prev/a·lence, prev/a·lent·ness, n. —prev/a·lent·ly, adv.

—Syn. 1. common, extensive. See current. —Ant. 1. rare.

pre·var·i·cate (pri var/ə kāt/), v.i., -cat·ed, -cat·ing. to speak falsely or misleadingly; deliberately misstate or create an incorrect impression; lie. [< L praevāricāt(us), ptp. of praevāricārī to walk as if straddling, (legal L: engage in collusion, eccl. L: transgress), equiv. to prae- PRE- + vāricāre to straddle, deriv. of vāricus straddling (vār(us) crooked, bent + -icus -IC)] —pre·var/i·ca/tion, n. —pre·var/i·ca/tive, pre·var·i·ca·to·ry (pri var/ə kə tôr/ē, -tōr/ē), adj.

—Syn. evade, shift.

pre·var·i·ca·tor (pri var/ə kā/tər), n. 1. one who prevaricates. 2. a Cambridge University student formerly delegated to give a satirical oration at commencement. Cf. terrae filius (def. 1). [< L: see PREVARICATE, -OR²]

pré·ve·nance (prāvᵉ näNs/), n., pl. -nances (-näNs/) for 2. French. 1. assiduity in anticipating or catering to the pleasures of others. 2. an instance of this.

pre·ven·ient (pri vēn/yənt), adj. 1. coming before; antecedent. 2. anticipatory. [< L praevenient- (s. of praeveniēns) coming before, prp. of praevenīre to anticipate. See PRE-, CONVENIENT] —pre·ve·nance (prev/ə nəns), pre·ven·ience (pri vēn/yəns), n. —pre·ven/ient·ly, adv.

preven/ient grace/, divine grace operating on the human will prior to its turning to God.

pre·vent (pri vent/), v.t. 1. to keep from occurring; hinder: He intervened to prevent bloodshed. 2. to hinder, as from doing something: There is nothing to prevent us from going. 3. Archaic. to act ahead of; forestall. 4. Archaic. to precede. 5. Archaic. to anticipate. —v.i. 6. to interpose a hindrance: He will come if nothing prevents. [ME < L praevent(us) started beforehand (ptp. of praevenīre to anticipate), equiv. to prae- PRE- + ven- (s. of venīre to come) + -tus ptp. suffix] —pre·vent/a·bil/i·ty, n. —pre·vent/a·ble, pre·vent/i·ble, adj. —pre·vent/ing·ly, adv.

—Syn. 1. obstruct, forestall, preclude, obviate, thwart. PREVENT, HAMPER, HINDER, IMPEDE refer to different degrees of stoppage of action or progress. To PREVENT is to stop something effectually by forestalling action and rendering it impossible: to prevent the sending of a message. To HAMPER is to clog or entangle or put an embarrassing restraint upon: to hamper preparations for a trip. To HINDER is to keep back by delaying or stopping progress or action: to hinder the progress of an expedition. To IMPEDE is to make difficult the movement or progress of anything by interfering with its proper functioning: to impede a discussion by demanding repeated explanations. —Ant. 1. help, assist.

pre·vent·er (pri ven/tər), n. 1. one who or that which prevents. 2. Naut. a. any of various lines set up to reinforce or relieve ordinary running or standing rigging. b. a line for preventing a sail from jibing. [PREVENT + -ER¹]

prevent/er back/stay, Naut. See jumper stay. Also called prevent/er stay/.

pre·ven·tion (pri ven/shən), n. 1. the act of preventing; effectual hindrance. 2. a preventive: This serum is a prevention against disease. [< LL praeventiōn- (s. of praeventiō) a forestalling. See PREVENT, -ION]

pre·ven·tive (pri ven/tiv), adj. 1. Med. of or noting a drug, vaccine, etc., for preventing disease; prophylactic. 2. serving to prevent or hinder: preventive medicine. —n. 3. Med. a drug or other substance for preventing disease. 4. a preventive agent or measure. Also, pre·vent·a·tive (pri ven/tə tiv) (for defs. 2, 4). [PREVENT + -IVE] —pre·ven/tive·ly, adv. —pre·ven/tive·ness, n.

preven/tive deten/tion, Eng. Law. imprisonment of a habitual criminal for periods ranging from 5–14 years during which he is given corrective training or placed under psychiatric and medical care.

preven/tive law/, Law. that part of office practice that attempts to anticipate and prevent future disappointment or controversy.

pre·ven·to·ri·um (prē/ven tôr/ē əm, -tōr/-, -vən-), n., pl. -to·ri·a (-tôr/ē ə, -tōr/-), -to·ri·ums. an institutional home for persons, esp. children, who might otherwise be exposed at their own homes to relatives having contagious or infectious diseases. [PREVENT + -ORIUM]

pre·view (prē/vyōō/), n. 1. an earlier or previous view. 2. an advance showing of a motion picture, play, ...to advertise its coming performance. 4. anything that gives an advance idea or impression of something to come. —v.t. 5. to view or show beforehand or in advance. Also, prevue. [PRE- + VIEW]

pre·vi·ous (prē/vē əs), adj. 1. coming or occurring before something else; prior: the previous owner. 2. Informal. done, occurring, etc., before the proper time; premature: Aren't you a little previous with that request? 3. previous to, before; prior to: Previous to her marriage she was a fashion model. [< L praevius going before, equiv. to prae- PRE- + vi(a) way + -us adj. suffix] —pre/vi·ous·ly, adv. —pre/vi·ous·ness, n.

—Syn. 1. earlier, former, preceding, foregoing. —Ant. 1. later.

pre/vious ques/tion, Parl. Proc. the question whether a vote shall be taken at once on a main question; moved before the main question is put and resorted to, esp. in the U.S., in order to cut off debate.

pre·vise (pri vīz/), v.t., -vised, -vis·ing. 1. to foresee. 2. to forewarn. [< L praevīs(us) foreseen, ptp. of praevidēre. See PRE-, VISA] —pre·vi/sor, n.

pre·vi·sion (pri vizh/ən), n. 1. foresight, foreknowledge, or prescience. 2. a prophetic or anticipatory vision or perception. [PRE- + VISION] —pre·vi/sion·al, adj.

pre·vo·cal·ic (prē/vō kal/ik), adj. Phonet. immediately preceding a vowel. [PRE- + VOCALIC] —pre/vo·cal/i·cal·ly, adv.

pre·vo·ca·tion·al (prē/vō kā/shə nᵊl), adj. of, pertaining to, or constituting preliminary vocational training. [PRE- + VOCATIONAL]

Pré·vost (prā vō/), n. Mar·cel (mar sel/), 1862–1941, French novelist and dramatist.

Pré·vost d'Ex·iles (prā vō/ deg zēl/), An·toine Fran·çois (äN twan/ fräN swa/), ("Abbé Prévost"), 1697–1763, French novelist.

pre·vue (prē/vyōō/), n., v.t., -vued, -vu·ing. preview.

Prew (prōō), n. a boy's given name.

pre·war (prē/wôr/), adj. before the war: prewar prices. [PRE- + WAR¹]

Prew·ett (prōō/it), n. a boy's given name, form of Prew. Also, Prew/itt, Pruett, Pruitt.

prex·y (prek/sē), n., pl. prex·ies. Slang. a president, esp. of a college or university. Also, prex. [prex (by shortening and alter. of president) + -Y²]

prey (prā), n. 1. an animal hunted or seized for food, esp. by a carnivorous animal. 2. a person or thing that is the victim of an enemy, a swindler, a disease, or the like. 3. the action or habit of preying: beast of prey. 4. Archaic. booty or plunder. —v.i. 5. to seize and devour prey, as an animal does (usually fol. by on or upon): Foxes prey on rabbits. 6. to make raids or attacks for booty or plunder: The Vikings preyed on coastal settlements. 7. to exert a harmful or destructive influence: His worries preyed upon his mind. 8. to victimize a class of persons (usually fol. by on or upon): loan sharks that prey upon the poor. [ME preye < OF < L praeda booty, prey] —prey/er, n.

Pri·am (prī/əm), n. Class. Myth. 1. a king of Troy, the son of Laomedon, husband of Hecuba, and father of many others. Paris, Cassandra, Hector, Polyxena, and many others. He was killed during the capture of Troy. 2. the grandson of King Priam.

Pri·a·mid (prī/ə mid), n. Class. Myth. any of the 50 sons of Priam.

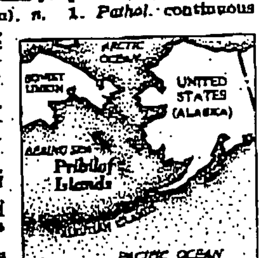
pri·a·pe·an (prī/ə pē/ən), adj. priapic. [< F priapéen < L Priāpē(ius) < Gk Priápeios. See PRIAPUS, -AN]

pri·ap·ic (prī ap/ik), adj. 1. (sometimes cap.) of or pertaining to Priapus; phallic. 2. characterized by or emphasizing a phallus: priapic figurines used in fertility rites. 3. (of an image) suggestive of or resembling a phallus by its shape. 4. exaggeratedly concerned with masculinity and male sexuality. [PRIAP(US) + -IC]

pri·a·pism (prī/ə piz/əm), n. 1. Pathol. continuous erection of the penis, esp. due to disease. 2. prurient behavior or display. [PRIAP(US) + -ISM] —pri/a·pis/mic, adj.

pri·a·pi·tis (prī/ə pī/tis), n. Pathol. inflammation of the penis. [PRIAP(US) + -ITIS]

Pri·a·pus (prī ā/pəs), n. 1. Class. Myth. a god of male procreative power, the son of Dionysus and Aphrodite. 2. (l.c.) a phallus.



Prib/i·lof Is/lands (prib/ə lof/), a group of islands in the Bering Sea, SW of Alaska, and belonging to the U.S.: the breeding ground of fur seals.

...i., -fied, -fy·ing.
...y, n.; pl. -sies.
...ving, adj.
...al, adj.
...adj.
...tion, -tir·ing.
...adj.
...t., -tured,
...ent, n.
...t., -traced,
...adj.
...al, adj.

pre/tran·scribe/, v.t., -scribed, -scrib·ing.
pre/tran·scrip/tion, n.
pre/trans·late/, v.t., -lat·ed, -lat·ing.
pre/trans·la/tion, n.
pre/trans·mis/sion, n.
pre/trans·mit/, v.t., -mit·ted, -mit·ting.
pre/trans·port/, v.t.
pre/trans·por·ta/tion, n.
pre·trav/el, n., v., -eled, -el·ing, or (esp. Brit.) -elled, -el·ling.
pre·trib/al, adj.
pre/-Tri·den/tine, adj.
pre·tro/chal, adj.
pre·try/, v.t., -tried, -try·ing.
pre-Tu/dor, adj.
pre/tym·pan/ic, adj.
pre·ty/phoid, adj.
pre/ty·po·graph/i·cal, adj.
pre/ty·ran/ni·cal, adj.
pre·tyr/an·ny, n.
pre·um/bo·nal, adj.
pre/un·der·stand/, v., -stood, -stand·ing.

pre/un·der·take/, v.t., -took, -tak·en, -tak·ing.
pre·un/ion, adj.
pre/u·nite/, v.t., -nit·ed, -nit·ing.
pre·u/ti·liz/a·ble, adj.
pre/u·ti·li·za/tion, n.
pre·u/ti·lize/, v.t., -lized, -liz·ing.
pre·va/cate, v.t., -cat·ed, -cat·ing.
pre/va·ca/tion, n., adj.
pre·vac/ci·nate/, v.t., -nat·ed, -nat·ing.
pre/vac·ci·na/tion, n.
pre·val/id, adj.; -ly, adv.
pre/va·lid/i·ty, n.
pre/val·u·a/tion, n.
pre·val/ue, v.t., -ued, -u·ing; n.
pre/var·i·a/tion, n.
pre/veg·e·ta/tion, n.
pre·ven/tral, adj.
pre·ven/ture, n., v., -tured, -tur·ing.
pre·ver/bal, adj.
pre/ver·i·fi·ca/tion, n.
pre·ver/i·fy/, v.t., -fied, -fy·ing.

pre·ver/sion, n.
pre·ver/te·bral, adj.
pre·ve/to, n., pl. -toes; v.t., -toed, -to·ing.
pre/-Vic·to/ri·an, adj.
pre/vic·to/ri·ous, adj.
pre·vig/i·lance, n.
pre·vig/i·lant, adj.; -ly, adv.
pre·vi/o·late/, v.t., -lat·ed, -lat·ing.
pre/vi·o·la/tion, n.
pre/-Vir·gil/i·an, adj.
pre/vis·i·bil/i·ty, n.
pre·vis/i·ble, adj.; -bly, adv.
pre·vis/it, n., v.
pre·vis/i·tor, n.
pre·vogue/, n.
pre·void/, v.t.
pre·void/ance, n.
pre/vo·li/tion·al, adj.
pre/-Vol/stead, n.
pre/vol·un·teer/, n., v.
pre·vote/, n., v., -vot·ed, -vot·ing.
pre·warm/, v.t.
pre·warn/, v.t.

pre·war/rant, n., v.t.
pre·wash/, n., v.t.
pre·weigh/, v.t.
pre·wel/come, n., v.t., -comed, -com·ing.
pre·whip/, v.t., -whipped, -whip·ping.
pre·will/ing, adj.; -ly, adv.; -ness, n.
pre·wire/, v.t., -wired, -wir·ing.
pre·wire/less, adj.
pre·wit/ness, n., v.t.
pre·world/li·ness, n.
pre·world/ly, adj.
pre·wor/ship, n., v., -shiped or -shipped, -ship·ing or -ship·ping.
pre·wor/thi·ly, adv.
pre·wor/thi·ness, n.
pre·wor/thy, adj.
pre·wound/, n., v.t.
pre·wrap/, v.t., -wrapped, -wrap·ping.
pre·youth/ful, adj.
pre/zy·go·mat/ic, adj.

...NUNCIATION KEY: act, āble, dâre, ärt; ebb, ēqual; if, īce; hot, ōver, ôrder, oil, bŏŏk, ōōze, out; up, ûrge; chief; sing; shoe; thin, that; zh as in measure. ...alone, e as in system, i as in easily, o as in gallop, u as in circus; ᵊ as in button (butᵊn), fire (fīᵊr), cradle (krādᵊl). See the full key inside the front cover.